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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/759,280

01/20/2004

Joanne Peart

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WHITHAM, CURTIS & CHRISTOFFERSON & COOK, P.C.

11491 SUNSET HILLS ROAD

SUITE 340

RESTON, VA 20190

EXAMINER

ALSTRUM ACEVEDO, JAMES HENRY

ART UNIT

PAPER NUMBER

1616

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

01/09/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/759,280	<b>Applicant(s)</b> PEART ET AL.	
	<b>Examiner</b> James H. Alstrum-Acevedo	<b>Art Unit</b> 1616	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 October 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 23, 25-48, 50 and 52-55 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 23, 25-48, 50, and 52-55 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

**Claims 23, 25-48, 50, and 52-55 are pending.** Applicants cancelled claims 24 and 51. Receipt and consideration of Applicant's amended claims, arguments/remarks, and the declaration of Dr. Jeffry G. Weers filed under 37 C.F.R. 1.132, all submitted on April 4, 2006, is acknowledged. The finality of the previous office action mailed on June 15, 2006 is hereby withdrawn based upon the decision of a pre-appeal conference held on October 24, 2006.

### ***Specification***

The objections of the specification for (a) the incorporation of foreign reference WO 01/03690 on page 18 of the disclosure and (b) minor informalities (see page 2 of the previous office action) **are withdrawn**, because said reference has been removed from the specification and the minor informality has been corrected.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

The rejection of claims 24, 30-36, and 41-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn**, per Applicant's amendments to the claims.

### ***Claim Rejections - 35 USC § 103***

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 23, 26-28, 30-35, 37-44, 46-48, 50, and 53-55 under 35 U.S.C. 103(a) as being unpatentable over Mechoulam et al. (U.S. Patent No. 5,804,592) or Volicer (U.S. Patent No. 5,804,592) in view of McNally et al. (U.S. Patent No. 5,653,961) is maintained. Applicant has cancelled claims 24 and 51.

The rejection of claim 36 under 35 U.S.C. 103(a) as being unpatentable over Mechoulam et al. (U.S. Patent No. 5,804,592) or Volicer (U.S. Patent No. 5,804,592) in view of McNally et al. (U.S. Patent No. 5,653,961) as applied to claims 23, 24, 26-28, 30-35, 37-44, 46-48, 50, 51, and 53-55 above, and further in view of *Workshop on the Medical Utility of Marijuana* (IDS: page 4, 2<sup>nd</sup> paragraph in the section entitled "Appetite Stimulation/Cachexia." National Institutes of Health, August 1997) is maintained.

The rejection of claims 25, 45, and 52 under 35 U.S.C. 103(a) as being unpatentable over Mechoulam et al. (U.S. Patent No. 5,804,592) or Volicer (U.S. Patent No. 5,804,592) in view of McNally et al. (U.S. Patent No. 5,653,961) as applied to claims 23, 24, 26-28, 30-35, 37-44, 46-48, 50, 51, and 53-55 above, and further in view of Pars et al. (U.S. Patent No. 3,728,360) is maintained.

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The rejection of claim 29 under 35 U.S.C. 103(a) as being unpatentable over Mechoulam et al. (U.S. Patent No. 5,804,592) or Volicer (U.S. Patent No. 5,804,592) in view of McNally et al. (U.S. Patent No. 5,653,961) as applied to claims 23, 24, 26-28, 30-35, 37-44, 46-48, 50, 51, and 53-55 above, and further in view of Ohlsson, A. *et al.* (*Clin. Pharmacol. Ther.* 28, 409-416) **is maintained**. Applicant has cancelled claims 49 and 56.

The rejection of claims 43-48, 50, and 52-55 under 35 U.S.C. 103(a) as being unpatentable over Pars et al. (U.S. Patent No. 3,728,360) in view of McNally et al. (U.S. Patent No. 5,653,961) **is maintained**. Applicant has cancelled claim 51.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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The rejection of claims 26-29, 43, 44, 46, 48, 50, and 52-55 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,509,005 (USPN '005) **is maintained**. Applicant has cancelled claims 24, 49, and 56.

### ***Response to Arguments***

Applicant's arguments filed April 4, 2006 have been fully considered but they are not persuasive. The declaration of Dr. Jeffrey G. Weers filed under 37 C.F.R. 1.132, submitted on April 4, 2006, has been considered, but was found insufficient. Applicant's traversal of the prior art rejections under 35 U.S.C. § 103(a) and the declaration of Dr. Weers rely on the assertion that a person of ordinary skill in the art would not have been motivated at the time of Applicant's invention to utilize hydrofluoroalkane (HFA) propellants in an inhalable formulation comprising tetrahydrocannabinol (THC), because of the previous difficulties of formulating THC in chlorofluorocarbons (CFC) and the extremely low solubility of other hydrophobic art recognized active agents in HFA propellants. The Examiner respectfully disagrees. The specific deficiencies, if any, of each section/paragraph of the declaration submitted April 4, 2006 (i.e. "Weers declaration") are addressed below, followed by the Examiner's position of the outstanding rejections in view of the Weers declaration.

Paragraph 1/section 1 merely states Dr. Weers' professional experience and sets forth his scientific education and qualifications. This paragraph/section fails to indicate what is the relationship both past and present between Dr. Weers and the inventors/assignee of the instant application. The declaration remains unconvincing.

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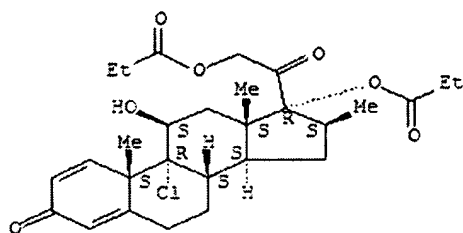
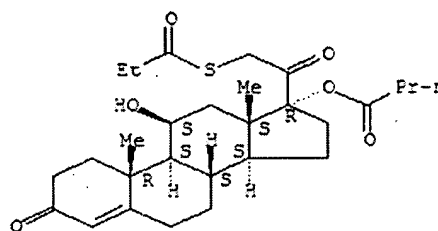
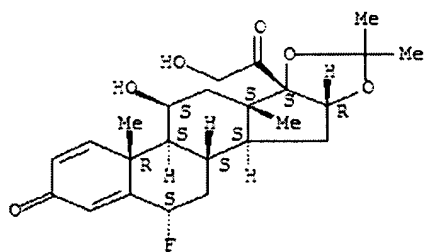
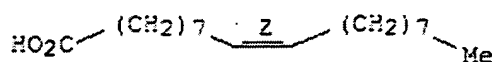
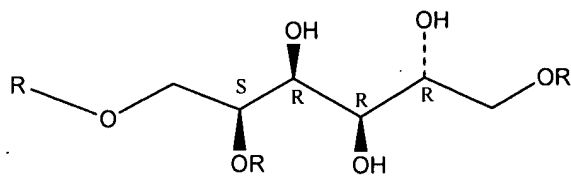
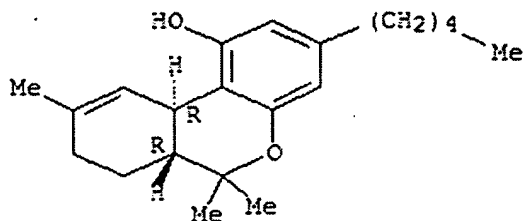
Paragraph 2/section 2 merely states Dr. Weers' opinion regarding the motivation of a person of ordinary skill in the art at the time of the instant invention. The opinion stated in paragraph 2/section 2 is not supported by any fact or evidence provided in said paragraph. The declaration remains unconvincing.

In paragraph 3/section 3, Dr. Weers asserts that an ordinary skilled artisan has at least a bachelor's degree in pharmaceuticals, and often would have an advanced degree such as a Ph.D. Dr. Weers opines that a person of ordinary skill in the art at the time of the instant invention would have had at least 8 years of hands-on experience working with propellants, such as CFCs and HFAs. Dr. Weers' opinion of the minimal amount of experience typical of a person of ordinary skill in the art is not supported by any facts or evidence and merely represents his best guess or estimate of the experience of an ordinary skilled artisan. Dr. Weers also does not explain why or how he determined that a person of ordinary skill in the art at the time of the instant invention would have had at least 8 years of hands-on experience. It is the Examiner's position that a person with at least 8 years of hands-on experience in a given field would not be an ordinary skilled artisan but an expertly skilled artisan. The declaration remains unconvincing.

In paragraph 4/section 4, Dr. Weers states that *in his opinion* "it would be particularly surprising and unexpected to one of ordinary skill in the art that the solubility of THC (tetrahydrocannabinol) in HFA propellants is high", when compared to the solubility of common bronchodilators, corticosteroids, and surfactants in HFA 134a. Dr. Weers' cites the solubility of butixocort propionate, beclomethasone dipropionate, and flunisolide hemihydrate in HFA 134a as being 0.02% w/w, 0.03% w/w, and less than 0.0006% w/w, respectively and provides reference citations where said solubilities are reported. According to Dr. Weers, the solubilities

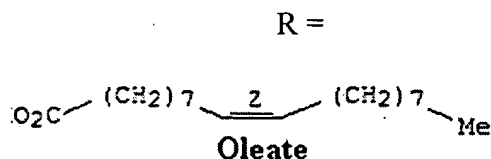
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of oleic acid and sorbitan trioleate surfactants reported in Blondino et al. (*Drug Dev. Ind. Pharm.* **1998**, 24, pp 935-945) are both less than 0.02% w/w. Dr. Weers also asserts that similar solubilities are observed in HFA 227, but does not cite any references to support this assertion. This paragraph/section suggests that all hydrophobic compounds exhibit similar intermolecular interactions that would limit solubility in HFA propellants. However, it is noted that all three specific examples of actives and the two specific surfactants cited by Dr. Weers have drastically different and varied chemical structures in comparison to THC (see structures below). Therefore,

**Beclomethasone Dipropionate****Butixocort Propionate**• 1/2 H<sub>2</sub>O**Flunisolide Hemihydrate****Oleic Acid****A Sorbitan Trioleate****Tetrahydrocannabinol**



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it would be an inappropriate comparison upon which to ascertain or estimate the solubility of THC in HFA 134a. Dr. Weers' also ignores the effect of cosolvents present in HFA propellants on the solubility of THC. The declaration remains unconvincing.

In paragraph 5/section 5, Dr. Weers describes the possible formulations that would have been considered by a person of ordinary skill in the art at the time of the instant invention for the preparation of THC HFA pharmaceutical compositions: (A) suspensions (i.e. criteria A in the Weers declaration) or (B) solutions. According to Dr. Weers' opinion suspension are not viable because THC cannot be processed to produce 2-3 micron-sized particles. Dr. Weers' fails to state why it is critical or necessary that suspension have particle sizes of 2-3 microns and why respirable particles sizes greater than 3 microns but less than 10 microns are not viable. Regarding solution formulations Dr. Weers states that the necessary criteria for suitable formulations are: (1) the formulations must be able to produce a significant percentage of respirable particles (i.e. droplets less than 10 microns in diameter) when aerosolized (criteria B in the Weers declaration); and (2) formulations must be chemically and physically stable for a significant period of time (i.e. these must have a useful "shelf life") (criteria (c) in the Weers declaration). Dr. Weers summarizes this section by stating that there are a variety of factors (i.e. suggesting there are variables/factors other than those mentioned by Dr. Weers that must be considered) impacting the three criteria (A)-(C). The discussion in this paragraph is vague, because it is unclear what a person of ordinary skill in the art at the time of the instant invention

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would consider (1) a significant percentage of respirable droplets; (2) a significant period of time; (3) a useful shelf-life; and (4) the other factors impacting ones ability to prepare HFA formulations of THC. Again Dr. Weers also fails to discuss formulations comprising (a) THC, (b) HFA propellant, and (c) solvent (e.g. ethanol) as is being claimed by Applicants and as is taught by the combined prior art. The declaration remains unconvincing.

In paragraph 6/section 6, Dr. Weers asserts that for a person of ordinary skill in the art it would have been an unexpected result that therapeutically feasible doses of THC are possible in HFA propellants, due to the newly discovered "high solubility" (i.e. 0.2% w/w in HFA 134a; See Table on page 4 of the Weers declaration) of THC in HFA 134a and HFA 227. Dr. Weers concedes that an ordinary skilled artisan would expect that addition of ethanol would be expected to increase THC solubility and then states that said artisan would know to minimize ethanol concentrations for toxicological reasons. Dr. Weers fails to state what amounts of ethanol a person of ordinary skill in the art would consider toxic. The data in the table on page 4 of the Weers declaration demonstrates the observed solubility of THC in various HFA 134a MDI formulations comprising 0 to "less than 15%" ethanol. Although Dr. Weers has provided data and examples of compounds with extremely low solubilities in HFA propellants, Dr. Weers has provided no standard by which a person of ordinary skill in the art would use to ascertain what is "low solubility", "average or regular solubility" and "high solubility." The data on page 4 of the Weers declaration clearly demonstrate what the Examiner has asserted and alluded in the previous office actions, based upon the teachings of the combined prior art, namely that a skilled artisan would have had a reasonable expectation that solution formulations comprising an HFA

propellant and ethanol could be used to prepare MDI compositions of THC. The declaration remains unconvincing.

In paragraph 7/section 7, Dr. Weers presents what he considers knowledge that would have been available to a person of ordinary skill in the art regarding MDI formulations and concludes that THC is a high dose non-volatile drug, presenting a significant formulation challenge that requires one to minimize the concentration of non-volatile ingredients (e.g. cosolvents and surfactants) to maximize the respirability of aerosols leaving the nozzle of an MDI (metered dose inhaler).

In paragraph 8/section 8, Dr. Weers states that a therapeutically effective dose of the oral form of THC (MARINOL<sup>®</sup>) is 2.5-5 mg, but that only 10% is bioavailable or absorbed systematically. Dr. Weers opines that Applicants' work represents a significant discovery because they have demonstrated that a therapeutically effective dose of THC may be delivered via inhalation. The data on page 6 of the Weers declaration demonstrate the dosage of THC delivered from 4 different "likely" formulations based upon the data in Applicants' Table 4b (see page 17 of the instant specification). Analysis based on speculative data (i.e. "likely formulations") is not persuasive. The declaration remains unconvincing.

In paragraph 9/section 9, Dr. Weers states that Applicants invention resolves a long-felt need in the art for inhalation formulations. According to Dr. Weers' citation from a 1999 report from the Institute of Medicine regarding the potential health benefits of marijuana and its constituent cannabinoids (see page 8 of the Weers declaration) concluded that (1) oral administration hampers the effectiveness of THC because of slow absorption and patients' desire to control dosing and that (2) [smoking] marijuana is a crude THC delivery system that

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simultaneously delivers harmful chemicals in addition to THC. Dr. Weers states, “interest in THC dates back nearly thirty years when efforts were focused on developing CFC propellant MDI to deliver THC to the lungs for treating asthma, no acceptable delivery systems of inhalation THC have been developed.” This section is deficient because it: (1) fails to indicate when the problem of developing pharmaceutically respirable HFA THC formulations and the need for said formulations was first identified and articulated; (2) fails to indicate the date of efforts to solve this problem using HFA propellant formulations; (3) fails to indicate that the lack of a solution to the “long-felt need” was not due to a lack of interest or lack of appreciation of an inventions’ potential or marketability, rather than a lack of technical know-how; (4) fails to provide evidence of prior unsuccessful attempts at making pharmaceutical HFA THC formulations; and (5) fails to provide evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP §716.04 [R-2]. The declaration remains unconvincing.

Paragraph/section 10 is merely Dr. Weers’ declaration that he believes his statements are made of his own knowledge and true; that statements made about information are believed to be true; and that he acknowledges the consequences of making willful false statements. The declaration remains unconvincing.

The Examiner’s position of the prior art teachings as they relate to the claimed subject matter in view of the above discussed declaration follow.

A person of ordinary skill in the art would have been motivated to prepare THC formulations utilizing HFA propellants instead of CFCs, because, as taught by McNally, CFCs

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were being phased out in favor of propellants, such as hydrofluorocarbons, which were known to be less harmful to the ozone layer. It is also noted that the McNally reference teaches a respirable fraction ranging from 45-69%, wherein the term "respirable fraction" is the percent by weight of particles having an aerodynamic particle size less than 4.7 microns. It is noted that the definition of respirable fraction in McNally lists "mm" as the unit of measurement, which the Examiner believes is a clear typographical error per what was well known in the art regarding respirable particle sizes (See, for example, Fig. 1 in Radhakrishnan et al. U.S. Patent No. 5,192,528). Furthermore, the advantages of inhalation administration and the necessity that inhaled active agent have particle sizes less than 5.8 microns for delivery to the deep lung, especially the alveoli, was well known in the art at the time of the instant invention, (See, for example, Fig. 1 in Radhakrishnan et al. U.S. Patent No. 5,192,528; and Burns et al. U.S. Patent No. 5,284,133 col. 5, lines 29-46).

Regarding the amount of ethanol recited by Applicant, the prior art teaches an overlapping amount of ethanol ranging from about 3 to about 30% by weight, thereby obviating Applicant's recitation of ethanol in an amount up to about 15% by weight. Routine optimization of the amount of ethanol in inhalable formulations would have yielded the amount necessary to dissolve THC and adhere to federal regulatory restrictions on maximum ethanol content.

In summary, the Examiner concludes that a person of ordinary skill in the art at the time of the instant invention would have found claims 23, 25-48, 50, and 52-55 *prima facie* obvious over the teachings of the combined prior art as discussed above in the instant office action and in the office actions mailed on 12/28/2005 and 6/15/2006. The Weers declaration does not alter the Examiners' conclusion regarding the obviousness of the pending claims.

*Conclusion*

**Claims 23, 25-48, 50, and 52-55 are rejected. No claims are allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0664. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

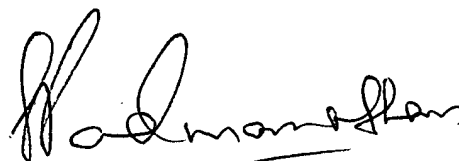
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may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo, Ph.D.  
Patent Examiner  
Technology Center 1600



Johann Richter, Ph. D., Esq.  
Supervisory Patent Examiner  
Technology Center 1600



SREENI PADMANABHAN  
SUPERVISORY PATENT EXAMINER